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THE COMBINED EFFECT OF CARBON MONOXIDE AND NORMOBARIC HYPEROXIA ON ANIMALS

Moscow KOSMICHESKAYA BIOLOGIYA I AVIAKOSMICHESKAYA MEDITSINA in Russian
No 6, 1978 pp 63-67

[Article by B. I. Abidin, V. I. Belkin, V. V. Kustov and A. N. Kondrat'yev, submitted 21 Sep 76]

[Text] The possibility of high oxygen content in the artificial atmosphere of small airtight spaces [1, 2] and the constant presence of low concentrations of carbon monoxide in it [3] are the reasons for the practical importance of investigating the combined effect on the organism of this chemical pollutant and normobaric hyperoxia, for the purpose of setting hygienic standards of levels thereof in the gas environment of such objects.

The results of such an investigation are submitted in this report.

Methods

In view of the objectives of this study, we selected a concentration of carbon monoxide (50.0±2.0 mg/m^3) and a level of partial oxygen pressure (320-340 mm Hg) in a normobaric gas environment which, in the case of 30 continuous days of exposure to it, would elicit demonstrable biological effects [3-5], so that it is possible to make a quantitative evaluation of the effects on the organism of each factor separately and to compare the findings to the effect of a combination of these factors.

The studies were conducted on 160 male albino rats with an initial weight of 160-170 g. The animals were divided into four groups. The first group was dynamically exposed to carbon dioxide in the above-mentioned concentration around the clock for 30 days; the second group of animals was put in a chamber with artificial gas environment at normal barometric pressure; partial oxygen pressure of 320-340 mm Hg was maintained automatically. The third group of rats was exposed to carbon monoxide in a concentration of 50.0±2.0 mg/m^3 in the above-mentioned hyperoxic gas environment for 30 days around the clock; the fourth group of animals was kept for 30 days in a chamber, through which room air was pumped.

Experimental and control rats were examined on the 10th, 20th and 30th experimental days. We recorded their weight, determined erythrocyte count and hemoglobin level in peripheral blood; we assayed carboxyhemoglobin in blood by the method of Wolff [6], Some rats from each group were decapitated for the study of activity of succinate dehydrogenase (KF [pharmacopeia] 1.3.99.1--succinate[acceptor]oxide reductase) and cytochromoxidase (KF 1.9.3.1--cytochrome-c:O_2-oxide reductase) of hepatic tissue [7, 8].

Results and Discussion

There were no deaths in any of the four groups of animals in the course of our experiments. At the same time, the selected concentration of carbon monoxide and normobaric hyperoxia induced certain changes in experimental animals, when exposed to these factors separately or in combination.

Throughout the 30-day observation period, the weight of rats (Figure 1) in the first, second and third groups was lower than in the fourth group (control). However, in the case of combined exposure to carbon monoxide and normobaric hyperoxia, this index differed less from the control than under the influence of each factor separately.

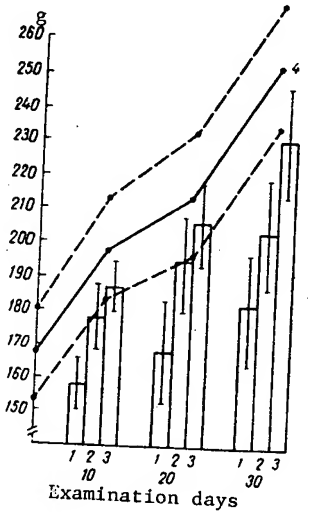

Figure 1.
Effect of separate and combined exposure to carbon monoxide and normobaric hyperoxia on weight dynamics of albino rats.

Here and in Figure 2:

1) normobaric hyperoxia
2) carbon monoxide
3) combination of hyperoxia and carbon monoxide

Determination of respiratory enzyme activity revealed the following: carbon monoxide had virtually no effect on activity of succinate dehydrogenase of the liver. The hyperoxic environment had an inhibitory effect on this

enzyme (on the 10th and 30th days), while exposure to carbon monoxide in a hyperoxic environment "smoothed" the inhibitory effect of the latter (Figure 2A).

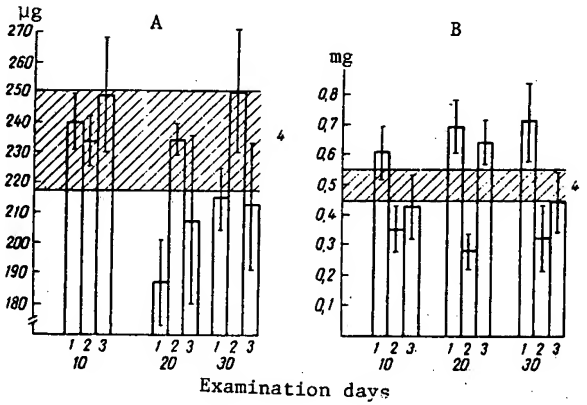

Figure 2. Activity of succinate dehydrogenase (A) and cytochromoxidase (B) of hepatic tissue of white rats under the separate and combined effects of carbon monoxide and normobaric hyperoxia

In the presence of the typical increase in cytochromoxidase activity in liver tissue under the influence of normobaric hyperoxia and depressing effect of carbon dioxide on this enzyme, in the case of combined exposure to both factors there was virtually no change in activity thereof (10th and 30th experimental days), or else it was appreciably greater than the "physiological norm," as established by us for many intact albino rats (Figure 2B).

The changes in hematological parameters (hemoglobin, erythrocyte count) of experimental animals (1st, 2d and 3d groups) were essentially in the range of physiological variability. However, the tendency toward erythrocytosis and hypergemoglobinemia, which was present with exposure to carbon monoxide alone, was absent in the case of exposure of animals to this toxic factor and normobaric hyperoxia (Table 1). The experimental conditions did not affect the carboxyhemoglobin level in blood of experimental and control rats (see Table 1).

The foregoing warrants the conclusion that the nature of the combined effect on the organism of relatively low, but hygienically significant in the case of continuous exposure for 30 days, levels of carbon monoxide and partial oxygen pressure in a normobaric artificial gas environment is determined by the antagonistic relations between the biological effects of the two factors (with prevalence of influence of one of them, or equal involvement of both) with respect to formation of a given recorded reaction (parameter).

Table 1. Effect of combination of carbon monoxide and normobaric hyperoxia on levels of erythrocytes, hemoglobin and carboxyhemoglobin in blood of experimental animals (M±m)

	Erythrocytes, million/mm³	Hemoglobin,

Table 1. Effect of combination of carbon monoxide and normobaric hyperoxia on levels of erythrocytes, hemoglobin and carboxyhemoglobin in blood of experimental animals (M±m)

Experimental conditions	Erythrocytes, million/mm^3				Hemoglobin, %				Carboxyhemoglobin, %			
	Examination days											
	Before exper.	10	20	30	Before exper.	10	20	30	Before exper.	10	20	30
Control	7,143±0,121	7,228±0,185	7,561±0,151	7,352±0,134	14,3±0,3	13,9±0,4	14,7±0,3	14,4±0,3	1,38±0,1	1,28±0,2	1,41±0,2	1,5 ±0,3
Carbon monoxide	7,258±0,133	7,730±0,106	8,552±0,125*	9,020±0,143*	12,9±0,2	15,3±0,5*	16,7±0,4*	16,9±0,3*	1,34±0,1	1,12±0,1	1,31±0,2	1,20±0,1
Hyperoxia	8,307±0,108	8,039±0,98	7,697±0,174	8,116±0,169	13,8±0,3	13,2±0,2	13,5±0,2	12,7±0,4	1,64±0,2	1,44±0,2	1,54±0,3	1,24±0,1
Carbon monox. & hyperoxia	7,300±0,211	6,821±0,189	7,182±0,162	7,310±0,193	14,8±0,4	14,8±0,2	15,0±0,3	15,0±0,4	1,41±0,3	1,49±0,2	1,41±0,2	1,25±0,3

*The results are reliable ($P<0.05$).

Table 2. Degree of effect of combination of carbon monoxide and normobaric hyperoxia on some of the parameters studied, %

	Weight			Hemoglobin			Erythrocytes			Cytochromoxidase activity			Succinate dehydrogenase act.		
	days														
	10	20	30	10	20	30	10	20	30	10	20	30	10	20	30
Carbon monoxide (factor A)	8,9	7,3	8,4	26,0	23,6	28,9	0,2*	6,7*	12,9	56,5	9,4	45,9	25,0	13,8	16,6
Hyperoxia (factor B)	26,6	29,5	5,8	15,7	25,2	40,0	11,1	21,2	18,7	14,6	56,9	24,1	0,03*	31,4	31,6
AB combination	38,8	42,2	51,9	11,0	10,8	5,3	2,2*	0,4*	7,6	0,2*	15,8	0,8*	0,09*	0,8*	2,8*
A+B+AB	73,4	79,0	66,1	52,8	59,6	74,2	13,5*	28,3	39,2	71,3	82,1	70,8	25,1	46,0	51,0
Random factors	25,7*	21,0*	33,9*	47,2*	40,4*	34,6*	86,5*	71,7*	60,8*	28,7*	17,9*	29,2*	74,9*	54,0*	49*

*The results are unreliable ($P>0.05$).

The experimental results were processed by the method of variance analysis [9, 10] for quantitative evaluation of this influence, and they are submitted in Table 2.

Table 2 shows that the share of involvement of organized experimental factors (A+B+AB) and random factors was not the same in formation of the selected parameters. Thus, the former prevailed over the latter in their effect on the weight of growing rats, hemoglobin content of peripheral blood and cytochromoxidase activity of hepatic tissue. Conversely, with regard to the effect on erythrocytes, random factors had a greater influence than the factors considered in the experiment. The influence of both factors under discussion on succinate dehydrogenase activity of hepatic tissue of experimental animals was virtually the same (with the exception of the 10th observation day). For this reason, we made a qualitative evaluation of the results on the basis of indices, the formation of which is substantially less affected by random factors than organized experimental factors. However, in addition to these indices, we also took into consideration the resultant tags, on which the factors studied had less influence than non-organized ones, especially since, in such cases, the statistical significance of the former was quite high ($P<0.05$). The results of this evaluation revealed that, in the case of combined exposure to carbon monoxide and normobaric hyperoxia, the influence of the latter (factor B) on the weight of growing rats (and, to some extent, on erythrocyte level in blood) not only was reliably related to the additional effect of carbon monoxide (factor A), but prevailed substantially on the 10th and 20th experimental days (26.6 and 29.5%, versus 8.9 and 7.3% for carbon monoxide). Both factors had virtually the same influence on hemoglobin level of peripheral blood of experimental rats.

Each of the organized factors alternately acquired and lost its predominant significance in the combined influence of both on the activity of respiratory enzymes. For example, on the 10th experimental day, carbon monoxide had a predominant influence on cytochromoxidase activity of hepatic tissue (56.59 versus 14.6% for hyperoxia); on the 20th observation day, on the contrary, the share of hyperoxia's effect rose to 56.9% and that of carbon monoside dropped to 9.4%; on the 30th experimental day, carbon monoxide again took over in the overall effect (45.9, versus 24.1% for hyperoxia). This difference in involvement of the factors tested in the selected responses of the organism stresses the necessity and, at the same time, serious difficulty of selecting a criterion that could be used to identify the type of combined action of chemical compounds at different experimental stages and, on this basis, to offer practical recommendations for differentiated setting of hygienic standards of levels thereof in an artificial gas environment.

V. V. Kustov et al. [11] suggested that one be governed, in such cases, by criteria reflecting the specific distinctions of toxic effect of the substances under study and, when it is difficult to choose such a criterion, by indices that integrally reflect their influence on the organism as a whole. Of course, this does not only fail to rule out, it even implies the use of

other parameters characterizing different aspects of biological effects of substances, for the purpose of objective evaluation of the nature of their combined effect.

Analysis of the results of these studies from the standpoint of the above theses leads to the conclusion that, according to most of the criteria used, the combined effect on the organism of carbon monoxide in a concentration of 50.0±2.0 mg/m[and artificial gas environment with elevated partial oxygen pressure, with continuous exposure for 30 days, is characterized by antagonism of their biological effects, with some prevalence of the influence of the latter over that of carbon monoxide. The foregoing warrants the belief that maximum permissible concentrations of each factor can be used, when an organism is exposed to both simultaneously, without any correction of these concentrations.

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